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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/557,423	04/21/2000	Boris P. Belotserkovskii	A-68112-1/RFT/RMS/DSS	6773

7590

03/12/2003

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EXAMINER

LOEB, BRONWEN

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 03/12/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/557,423

Applicant(s)

BELOTSEKOVSKII ET AL.

Examiner

Bronwen M. Loeb

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 December 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 43-45, 52-66, 108, 112 and 113 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 43-45, 52-66, 108, 112 and 113 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 April 2000 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: flyer re: Revised Format Permitted for Amendments.

DETAILED ACTION

This action is in response to the amendment filed 23 December 2002 in which claims 43, 44, 60, 64, 108, 112 and 113 were amended.

Claims 43-45, 52-66, 108, 112 and 113 are pending.

Drawings

1. New corrected drawings are required in this application because of the objections set forth in the Form 948 attached to the action mailed 15 June 2002. Applicant is advised to employ the services of a competent patent draftsman outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Response to Amendment

2. The rejection of claims 60-63 under 35 USC §112, second paragraph as being indefinite has been withdrawn in view of Applicant's amendment.

The rejection of claims 44 and 64-66 under 35 U.S.C. §112, second paragraph, as being indefinite has been withdrawn in view of Applicant's amendment.

The rejection of claims 43, 52, 54-56, 60-63, 108 and 113 under 35 U.S.C. §102(b) as being anticipated by Sena et al (USP 5,273,881) has been withdrawn in view of Applicant's amendment.

3. Claims 43, 52-66, 108 and 113 stand rejected under 35 U.S.C. §102(e) as being anticipated by Pati et al (USP 5,948,653).

Claims 43, 52-66, 108, 112 and 113 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Pati et al.

Claims 43, 45, 52-66, 108, 112 and 113, and claim 44, stand rejected under 35 U.S.C. 103(a) as being unpatentable over Pati et al as applied to claims 43, 52-66, 108, 112 and 113 above, and further in view of Helene et al (Biochimica et Biophysica Acta (1990) 1049:99-125).

Claims 43, 45, 52-66, 108, 112 and 113 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Pati et al as applied to claims 43, 52-66, 108, 112 and 113 above, and further in view of Barton (USP 5,225,556).

Claims 43, 45, 52-66, 108, 112 and 113, and claim 44, stand rejected under 35 U.S.C. §103(a) as being unpatentable over Pati et al as applied to claim claims 43, 52-66, 108, 112 and 113 above, and further in view of Simonsson et al (Nucleic Acids Research (1998) 26:1167-1172).

4. New grounds of rejection, necessitated by Applicant's amendment, are set forth below.

Response to Arguments

5. With regard to the rejection of: claims 43, 52-66, 108 and 113 under 35 U.S.C. §102(e) as being anticipated by Pati et al; claims 43, 52-66, 108, 112 and 113 under 35 U.S.C. §103(a) as being unpatentable over Pati et al; claims 43-45, 52-66,

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108, 112 and 113 under 35 U.S.C. 103(a) as being unpatentable over Pati et al as applied to claims 43, 52-66, 108, 112 and 113 above, and further in view of Helene et al; claims 43, 45, 52-66, 108, 112 and 113 under 35 U.S.C. §103(a) as being unpatentable over Pati et al as applied to claims 43, 52-66, 108, 112 and 113 above, and further in view of Barton; and claims 43-45, 52-66, 108, 112 and 113 under 35 U.S.C. §103(a) as being unpatentable over Pati et al as applied to claim claims 43, 52-66, 108, 112 and 113 above, and further in view of Simonsson et al, Applicant's arguments have been fully considered but are deemed not persuasive.

Pati et al teach a composition comprising at least one recombinase and a double D-loop comprising a target nucleic acid and a single stranded targeting polynucleotide comprising a first homology clamp, a second homology clamp and at least one anchoring sequence. Pati et al teach the composition above further comprising a second single stranded targeting polynucleotide. See col. 19, line 61-col. 20, line 3, col. 22, lines 31-59, Figures 10, 13B, and 13C, and ex.5, col. 53-58, wherein the "locking sequence" in the instant specification reads on the "internal homology clamp" of Pati et al and wherein Figure 13B, for instance, illustrates a single stranded targeting polynucleotide comprising a first and second homology clamp and at least one anchoring sequence. The internal homology clamp taught by Pati has duplex secondary structure comprising Watson-Crick base pairs. The composition wherein the nucleic acids may be DNA, RNA or a hybrid of both is taught in col. 16, lines 19-30. The composition wherein the recombinase is a prokaryotic recombinase is taught in col. 23, line 35- col. 24, line 8 and wherein the recombinase is prokaryotic RecA protein and

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wherein the RecA is from E. coli is taught in col. 24, lines 8-15. The composition wherein the recombinase is an eukaryotic recombinase is taught in col. 24, lines 15-20 and wherein it is Rad51 is taught in col. 24, lines 19 and 30. The composition wherein the eukaryotic recombinase is a complex of recombinase proteins is taught in col. 24, lines 22-23. The composition where at least one single stranded nucleic acid contains at least one substituent is taught in col. 7, lines 17-29 and col. 27, lines 40-42. The composition wherein the substituent is a chemical substituent is taught in col. 27, line 40- col. 28, line 5 and wherein the substituent is a protein is taught in col. 27, lines 58-59 and 65. The composition wherein the substituent is selected from the group consisting of intercalators, cross-linking moieties, labels, photoactive moieties, nucleic acid scission inducing moieties, purification moieties and nucleic acid modification moieties is taught in col. 27, lines 40-col. 28, lines 24. A cell containing the composition is taught in col. 28, lines 65-67, wherein the cell is eukaryotic is taught in col. 29, lines 63-65 and wherein it is prokaryotic is taught in col. 29, line 28. A kit comprising at least one recombinase and two substantially complementary single stranded targeting polynucleotides, each containing at least two homology clamps and at least one locking sequence is taught in col. 35, lines 58-59.

Pati et al does not explicitly disclose a composition wherein a protein is bound to the anchoring sequence. Pati et al teach the use of the composition to target chemical substituents to a predetermined DNA sequence using homologous pairing to produce sequence-specific localization of polynucleotides, for instance loading sites for transcription factors and/or RNA polymerase. See col. 7, lines 29-39. At the time the

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invention was made it would have been obvious to one of ordinary skill in the art to have the anchoring sequence encode a particular protein-binding site to which the protein would bind. One of ordinary skill in the art would be motivated to do this to increase the effective concentration of the protein in the vicinity of the targeted nucleic acid sequence, for instance, to increase the rate of homologous recombination or to enhance transcription repression with a repressor protein.

Pati et al does not explicitly teach: a composition further comprising a secondary probe, wherein said probe is substantially complementary to at least one of said anchoring sequences; a composition wherein said anchoring sequences form a triplex anchor. Helene et al teach providing a probe which forms a triplex structure as a means to regulate or stop transcription. See pp. 100-102 and Figures 1 and 3a. At the time the invention was made, it would have been obvious to one of ordinary skill in the art to use the probe of Helene et al in the composition of Pati et al, and to use the triplex anchor taught by Helene et al in the composition of Pati et al. One would have been motivated to do so since both references deal with methods of gene regulation using complementary DNA sequences. See Pati et al, col. 8, line 54-col. 9, line 2, and Helene et al, pp. 99-100 Introduction.

Pati et al does not teach a composition wherein the locking sequences form a Z-DNA anchor; a composition wherein the locking sequences form an A-DNA anchor. Barton teaches a chemical probe specific for Z-DNA sequences and A-DNA sequences that may be used for labeling Z-DNA or A-DNA sequences. See Abstract, col. 4, lines 31-34, and col. 5, lines 26-30 and 34-37. At the time the invention was made, it would

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have been obvious to one of ordinary skill in the art to use locking sequences that form Z-DNA or A-DNA. One of ordinary skill in the art would have been motivated to do so in order to use the specific chemical probe of Barton in order to label specifically the complexes formed by the composition with the target nucleic acid.

Pati et al does not teach the composition wherein the anchoring sequences form a quadruplex anchor. At the time the invention was made, it would have been obvious to one of ordinary skill in the art to use a quadruplex anchor in the composition of Pati et al. One would have been motivated to do so because it was well known that quadruplex sequences are very stable (see Simonsson et al, p.1169-1170, Discussion) and forming a stable multistrand complex to inhibit transcription is taught by Pati et al (col. 8, line 63-col. 9, line 3).

Applicant argues that the primary reference, Pati, is deficient. Specifically, Applicant argues that the double D loop taught by Pati is stabilized by Watson-Crick base pairing and that Applicant is unaware of any disclosure in Pati which teaches or suggests locking nucleic acids which confer secondary structure. As *one of ordinary skill in the art* knows, base pairing, particularly Watson-Crick base pairing, creates secondary structure in nucleic acids. While the most common secondary structure formed in DNA with Watson-Crick base pairing is B-form DNA (see Stryer, pp. 76-78), Watson-Crick base pairing is also in A-form and Z-form DNA (see Zubay, pp.665-676, especially pp. 671-673). It is noted that these references are from standard biochemistry textbooks, indicating the well known and acknowledged relationship between Watson-Crick base pairing and nucleic acid secondary structure. Thus, Pati

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inherently discloses secondary structure in the double D loop they teach. Furthermore, Applicant's specification teaches that their locking sequences (also called anchoring sequences) "form traditional duplexes (structures with Watson-Crick base pairing)" (p. 21, lines 4-7). The specification defines duplex structures on p. 20, lines 29-31 as "A-DNA, B-DNA, C-DNA, Z-DNA". Indeed, Applicant's amendment filed 23 July 2001 acknowledges this in part: "The locking sequences form non-Watson-Crick complexes such as triplexes, Z-DNA anchors or quadruplexes that prevent DNA rotation, thereby stabilizing the double D-Loop complex" (p. 13, under "The Invention"). As Zubay teaches, Z-DNA does in fact contain Watson-Crick base pairing, thus Applicant was mistaken with respect to Z-DNA. Therefore, Applicant's argument regarding Pati is not persuasive for any of the rejections as it is not deficient; in teaching Watson-Crick base pairing, Pati teaches traditional duplex secondary structure in their locking nucleic acids.

It is noted that claim 44 has now been included in some of the rejections. This rejection is necessitated by Applicant's amendment to claim 44, which was made in response to the rejection under 35 USC §112, second paragraph in the action mailed 15 June 2002.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 44, 45, 52-66 and 113 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 113 is vague and indefinite in reciting "a secondary structure" in line 7. Is this secondary structure different and separate from "a secondary structure" recited in claim 43, line 8?

Claim 45 recites the limitation "said locking sequences" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

Claims 43-45, 52-66, 108, 112 and 113 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 11:00 AM to 7:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

March 9, 2003


REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Revised Notice*

AMENDMENTS MAY NOW BE SUBMITTED IN REVISED FORMAT

The United States Patent and Trademark Office (USPTO) is permitting applicants to submit amendments in a revised format as set forth below. Further details of this practice are described in *AMENDMENTS IN A REVISED FORMAT NOW PERMITTED*, signed January 31, 2003, expected to be published in *Official Gazette* on February 25, 2003 (Notice posted on the Office's web site at <http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm>). The revised amendment format is essentially the same as the amendment format that the Office is considering adopting via a revision to 37 CFR 1.121 (Manner of Making Amendments). The revision to 37 CFR 1.121 (if adopted) will simplify amendment submission and improve file management. The Office plans to adopt such a revision to 37 CFR 1.121 by July of 2003, at which point compliance with revised 37 CFR 1.121 will be mandatory.

Effective immediately, all applicants may submit amendments in reply to Office actions using the following format. Participants in the Office's electronic file wrapper prototype¹ receiving earlier notices of the revised practice may also employ the procedures set out below.

REVISED FORMAT OF AMENDMENTS

Begin on separate sheets:

Each section of an Amendment (e.g., Claim Amendments, Specification Amendments, Drawing Amendments, and Remarks) should begin on a separate sheet. *For example*, in an amendment containing a.) introductory comments, b.) amendments to the claims, c.) amendments to the specification, and d.) remarks, each of these sections must begin on a separate sheet. This will facilitate the process of separately indexing and scanning of each part of an amendment document for placement in an electronic file wrapper.

Two versions of amended part(s) no longer required:

The current requirement in 37 CFR 1.121(b) and (c) to provide two versions (a clean version and a marked up version) of each replacement paragraph, section or claim will be waived where an amendment is submitted in revised format below. The requirements for substitute specifications under 37 CFR 1.125 will be retained.

A) Amendments to the claims:

Each amendment document that includes a change to an existing claim, or submission of a new claim, **must include a complete listing** of all claims in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.

- (1) The current status of all of the claims in the application, including any previously canceled or withdrawn claims, must be given. Status is indicated in a parenthetical expression following the claim number by one of the following: (original), (currently amended), (previously amended), (canceled), (withdrawn), (new), (previously added), (reinstated – formerly claim #_), (previously reinstated), (re-presented – formerly dependent claim #_), or (previously re-presented). The text of all pending claims under examination must be submitted each time any claim is amended. Canceled and withdrawn claims should be indicated by only the claim number and status.
- (2) All claims being currently amended must be presented with markings to indicate the changes that have been made relative to the immediate prior version. The changes in any amended claim should be shown by strikethrough (for deleted matter) or underlining (for added matter). An accompanying clean version is not required and should not be presented. Only claims of the status "currently amended" will include markings.
- (3) The text of pending claims not being amended must be presented in clean version, i.e., without any markings. Any claim text presented in clean version will constitute an assertion that it has not been changed relative to the immediate prior version.

¹ The Office's Electronic File Wrapper prototype program is described in *USPTO ANNOUNCES PROTOTYPE OF IMAGE PROCESSING*, 1265 Off. Gaz. Pat. Office 87 (Dec. 17, 2002) ("Prototype Announcement"), and applies only to Art Units 1634, 2827 and 2834.

- (4) A claim may be canceled by merely providing an instruction to cancel. Listing a claim as canceled will constitute an instruction to cancel. Any claims added by amendment must be indicated as (new) and shall not be underlined.
- (5) All of the claims in each amendment paper must be presented in ascending numerical order. Consecutive canceled or withdrawn claims may be aggregated into one statement (e.g., Claims 1 – 5 (canceled)).

Example of listing of claims (use of the word “claim” before the claim number is optional):

Claims 1-5 (canceled)

Claim 6 (withdrawn)

Claim 7 (previously amended): A bucket with a handle.

Claim 8 (currently amended): A bucket with a ~~green~~ blue handle.

Claim 9 (withdrawn)

Claim 10 (original): The bucket of claim 8 with a wooden handle.

Claim 11 (canceled)

Claim 12 (re-presented – formerly dependent claim 11) A black bucket with a wooden handle.

Claim 13 (previously added): A bucket having a circumferential upper lip.

Claim 14 (new): A bucket with plastic sides and bottom.

B) Amendments to the specification:

Amendments to the specification must be made by presenting a replacement paragraph or section marked up to show changes made relative to the immediate prior version. An accompanying clean version is not required and should not be presented. If a substitute specification is being submitted to incorporate extensive amendments, both a clean version (which will be entered) and a marked up version must be submitted as per current 37 CFR 1.125.

C) Amendments to drawing figures:

Drawing changes must be made by presenting replacement figures which incorporate the desired changes and which comply with § 1.84. An explanation of the changes made must be presented in the remarks section of the amendment. Any replacement drawing sheet must include all of the figures appearing on the immediate prior version of the sheet, even though only one figure may be amended. The figure or figure number of the amended drawing should **not** be labeled as “amended.” If the changes to the drawing figure(s) are not accepted by the examiner, applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless applicant is notified.

Any questions regarding the submission of amendments pursuant to the revised practice set forth in this flyer should be directed to the following legal advisors in the Office of Patent Legal Administration (OPLA): Elizabeth Dougherty (Elizabeth.Dougherty@uspto.gov), Gena Jones (Eugenia.Jones@uspto.gov) or Joe Narcavage (Joseph.Narcavage@uspto.gov). For information on the waiver or legal aspects of the prototype, please contact Jay Lucas (Jay.Lucas@uspto.gov), Senior Legal Advisor (PCTLA) or Rob Clarke (Robert.Clarke@uspto.gov), Senior Legal Advisor (OPLA). Alternatively, further information may be obtained by calling OPLA at (703) 305-1616.

* Revised Notice: See Sec. B) for changes relating to substitute specifications, and Sec. C) for changes on replacement drawing practice.